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Chapter XVI

CEREBRAL CIRCULATORY AND METABOLIC CHANGES ASSOCIATED WITH AGING[1]

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The widespread prevalence of vascular disease among the aged has led to major consideration of the role of the circulation in the pathogenesis of human aging. Since many of the most prominent clinical features of old age are attributable to changes in the central nervous system, studies of the cerebral circulation and metabolism in the aged have enjoyed considerable popularity in recent years (2–10). At the 1955 Annual Meeting of this Association, which was devoted to the topic of aging, Kety (11) reviewed the results of such studies in presumably normal elderly man. On the basis of the information available in the literature at that time, it was concluded that there is a small but nonetheless progressive decline in both cerebral blood flow and oxygen consumption with advancing age. There was no definitive evidence to indicate which was the primary change, the decline in cerebral blood flow or the reduction in cerebral metabolic rate. As Kety pointed out, however, these studies reflected "only an approximation of the normal aging process," for, although all patients with gross evidence of vascular disease, neurological disease, or senile psychosis were excluded from the studies, the remainder were drawn entirely from hospital populations; they included, therefore, a variety of diseases, even if they were of a type deemed unlikely to alter the cerebral circulation and metabolism. Furthermore, it was uncertain how successfully asymptomatic or minimal vascular disease may have been excluded from these studies, for such diseases are often so subtly intertwined with the aging process that they are extremely difficult to distinguish. Indeed, the view is not infrequently expressed that vascular pathological changes, such as those occurring in arteriosclerosis, are themselves part of the process of aging.

The present studies were undertaken to observe the effects of normal

[1] The studies described in this report represent only a portion of a project carried out in collaboration with Drs. Darab K. Dastur, Mark H. Lane, Douglas B. Hansen, Seymour S. Kety, Robert N. Butler, and Seymour Perlin. The project as a whole is to be described in detail elsewhere (1).

aging in man. The goal was to isolate and determine the effects of duration of life or chronological aging *per se*. Factors of health were, therefore, a prime consideration in these studies. Indeed, these studies were uniquely different from previous studies of this type only in regard to the rigorousness of the selection of subjects on the basis of health criteria. The ideal was to obtain a group of aged subjects as free from disease as the group of normal young adults studied for comparison. For operational purposes, all pathological changes which are occasionally observed in young individuals but do not occur uniformly in all aged members of the species were considered to reflect the influence of disease rather than normal aging. A corollary of this definition was the admittedly optimistic assumption that vascular disease is not an undissociable, integral part of the aging process but rather a disease which happens to occur with increasing frequency with advancing age. The basic question was whether, in the absence of vascular or any other type of disease, cerebral blood flow and metabolic rate decline as a consequence of chronological aging. In the event that such reductions were observed in these studies, as they had been in previous studies, it was hoped that evidence would be acquired to indicate which was the primary change: 1) a reduction in cerebral blood flow leading to cerebral hypoxia, tissue damage and a reduced cerebral metabolic rate or 2) a primary parenchymatous change in the brain manifested by a reduced cerebral metabolic rate followed by a secondary readjustment of the circulation to the reduced metabolic demand of the tissues. Finally, in view of the fact that these cerebral circulatory and metabolic studies were only one part of a broad multidisciplinary study of aging involving many investigators from various disciplines, it was hoped that possible relationships could be examined between the cerebral circulatory and metabolic functions and a variety of electroencephalographic, psychological, psychiatric and sociological variables. The multidisciplinary aspects of these studies are beyond the scope of this report but are presented in detail elsewhere (12).

METHODS

Subject Material. In order to minimize the influence of age-associated disease as much as possible, the subjects for these studies were drawn not from a hospital population as in previous studies, but rather from a group of volunteers aged 65 or more, who were living and functioning normally in their communities.[2] These volunteers were first given a careful medical screening in the field. Those who passed the initial screening were then

[2] Volunteers were obtained through the kind and helpful cooperation of the Home for the Jewish Aged, Philadelphia, Pennsylvania, and the National Association for Retired Civil Service Employees, Washington, D. C.

admitted to the National Institute of Mental Health (NIMH) for a 2-week period during which time they were subjected to a thorough and comprehensive series of clinical, laboratory and x-ray examinations designed to evaluate as precisely as possible the state of their health.[3] The medical evaluation procedures, medical characteristics of the sample and criteria for acceptance and classification are described in detail elsewhere (13). Screening of volunteers extended over a period of approximately 2 years, and of a large but indeterminate number of subjects, 54 passed the initial screening and were admitted to NIMH. Of these 54, 27 subjects fulfilled the rigid criteria for classification as normal elderly men. This group (group I) consisted of subjects without any symptoms or objective evidence of disease, doubtful evidence of minimal disease or definite evidence of truly trivial disease (*i.e.*, partial deafness, cataracts, varicose veins, or benign prostatic hypertrophy). In 20 subjects the medical examinations uncovered definite evidence of disease with more serious implications, but, since in these cases the disease was so minimal as to be asymptomatic, they were included in the study as a separate group (group II). The findings which distinguished subjects in group II from those in group I are indicated in table XVI.1. In most cases, the distinguishing features were related to vascular disease, for example, hypertension, arteriosclerosis or both. Seven of the 54 subjects exhibited definite evidence of serious, advanced or symptomatic disease and were, therefore, rejected outright from the study.

Cerebral circulatory and metabolic studies were successfully accomplished in 26 of the 27 subjects in group I and 17 of the 20 subjects in group II. Except for mean arterial blood pressure, none of the results of the research procedures played any part in the evaluation and classification of the elderly subjects into their respective groups. The normal range of mean arterial blood pressure was defined as the mean value $\pm$ 3 standard deviations (84 $\pm$ 23 mm. Hg) obtained during similar cerebral circulatory and metabolic studies performed simultaneously on a group of 15 normal young adults for the purpose of obtaining comparative data. On the basis of this definition, 5 elderly subjects who fulfilled all the clinical requirements for inclusion in group I were found to be hypertensive at the time of the cerebral blood flow measurements and were, therefore, relegated to group II. In addition to the previously described groups of elderly men and normal young subjects, a series of 10 patients suffering from chronic brain syndrome with psychosis were admitted from St. Elizabeths Hospital (Washington, D. C.) and Spring Grove Hospital (Catons-

[3] The medical evaluation program was carried out by Drs. Mark H. Lane and Thomas S. Yates with the aid of all the clinical facilities of the Clinical Center, National Institutes of Health, Bethesda, Maryland.

TABLE XVI.1

Diagnoses and diagnostic criteria in subjects in asymptomatic disease group

Diagnosis	Diagnostic Criteria
I. Vascular disease	
Hypertension	Sphygmomanometry or direct measurement in femoral artery with indwelling needle and Hg manometer
Arteriosclerosis	Electrocardiogram abnormalities such as conduction defects (bundle-branch blocks) and evidence of old myocardial infarction; absent peripheral pulses; x-ray evidence of aortic calcification and dilation or intracranial vascular calcification (in carotid siphon); ophthalmoscopic examinations showing retinal arteriosclerosis; senile tremors (minimal)
II. Gastrointestinal disease	
Duodenitis	
Questionable peptic ulcer	
III. Skeletal disease	
Minimal to moderate diffuse rheumatoid arthritis or osteoarthritis (no limitations in activity)	
IV. Metabolic disease	
Gout	Asymptomatic elevation of blood uric acid level
Diabetes mellitus (controlled by diet alone without insulin; only fasting hyperglycemia and abnormal glucose tolerance)	

ville, Maryland)[4] and studied in a similar fashion in order to investigate further the relationship between this clinical condition and cerebral circulatory and metabolic functions.

Experimental Procedures. Cerebral blood flow (CBF) was determined by the nitrous oxide technique of Kety and Schmidt (14). However, in anticipation of the possibility of low rates of cerebral blood flow in these subjects, the measurement period was extended from the usual 10 minutes to 15 minutes to allow more time for equilibration between brain tissue and mixed cerebral venous blood, an assumption essential to the validity

[4] The patients were made available through the courtesy of Dr. Edward D. Griffin, St. Elizabeths Hospital, and Drs. Isadore Tuerck and Albert Kurland, Spring Grove Hospital; we are indebted to Dr. William Pollin for the examination and selection of the patients.

of the method. Mean arterial blood pressure (MABP) was measured directly in the femoral artery by means of an air-damped mercury manometer adjusted to the level of the carotid artery; mean cerebral venous pressure was measured directly in the internal jugular vein by means of a Statham strain gauge (model P23B), Brush Universal Analyser (model BL-320) and oscillograph (model BL-202).

Blood oxygen and carbon dioxide contents were determined by the manometric method of Van Slyke and Neill (15); blood oxygen saturation was measured directly by the Triton X-100 spectrophotometric technique (16). Blood pH was measured anerobically at ambient temperature by means of a MacInnes-Belcher glass electrode and Cambridge potentiometer (model R) and was then corrected to its value at 37°C. by means of the factors of Rosenthal (17). Blood glucose concentration was measured by the Nelson-Somogyi method (18), and arterial hemoglobin concentration was determined by conversion to cyanmethemoglobin and photometric measurement (19).

The following functions were computed from the directly measured variables described above. Cerebral oxygen consumption (CMR_{O_2}) and glucose utilization (CMR_G) were calculated as the products of the CBF and the cerebral arteriovenous oxygen ($[A - V]_{O_2}$) and glucose ($[A - V]_G$) differences, respectively. The O_2-glucose ratio (O_2/G) was determined from the molar values of $(A - V)_{O_2}$ and $(A - V)_G$, and the cerebral respiratory quotient (CRQ) was obtained by division of the $(A - V)_{O_2}$ into the cerebral arteriovenous carbon dioxide difference. Cerebral vascular resistance (CVR), the ratio of cerebral blood pressure gradient to blood flow, was calculated by division of the difference between the mean arterial and the mean cerebral venous blood pressures by the CBF. Blood carbon dioxide tension (pCO_2) was determined by means of the nomogram of Van Slyke and Sendroy (20), and the nomogram based on the data of Dill (21) was employed for the determination of the internal jugular venous oxygen tension (pO_2).

RESULTS

In table XVI.2 are compared the values for cerebral circulatory functions obtained in the normal young, normal elderly and elderly with asymptomatic disease groups. The most striking feature of these results is that, except for the expected slight increases in mean arterial blood pressure and cerebral vascular resistance, there were no statistically significant differences between the normal young and normal elderly subjects, despite an approximately 50-year difference in their mean ages. On the other hand, in the elderly subjects with asymptomatic disease, there was

TABLE XVI.2

Cerebral circulation in normal young, normal elderly and elderly subjects with asymptomatic disease

Group	Number of Subjects	Age	Mean Arterial Blood Pressure	Cerebral Blood Flow	Cerebral Vascular Resistance	Cerebral Venous Oxygen Tension
		years	*mm.Hg.*	*ml./100gm./minute*	*mm.Hg/(ml./100 gm./minute)*	*mm.Hg*
Normal young	15	20.8 ± 0.4	84 ± 2	62 ± 3	1.3 ± 0.1	38 ± 1
Normal elderly	26	71.0 ± 0.8[1]	93 ± 1[1]	58 ± 2	1.6 ± 0.1[1,2]	36 ± 1
Elderly with miscellaneous asymptomatic disease	17	72.8 ± 1.5[1]	111 ± 5[1,2]	52 ± 3[1]	2.1 ± 0.1[1,2]	35 ± 1

[1] Statistically significantly different from normal young subjects ($p < 0.05$).

[2] Statistically significantly different from normal elderly men ($p < 0.05$).

a small but significant decline in cerebral blood flow below the level of the normal young subjects. The higher values for mean arterial blood pressure and cerebral vascular resistance observed in the asymptomatic disease group reflects the fact that this group was comprised chiefly of subjects with vascular disease, for example, hypertension or arteriosclerosis, or both. The cerebral venous pO_2, which probably indicates the level of oxygen tension in the cerebral tissues, tended to be reduced slightly in the normal elderly group and somewhat more so in the subjects with asymptomatic disease although in neither case was the change significant.

In table XVI.3 are presented the cerebral metabolic data obtained for these same groups. There was a tendency for the arteriovenous oxygen difference to rise and the cerebral oxygen consumption to fall in the elderly subjects, particularly the asymptomatic disease group, but these changes were not statistically significant. In contrast, the cerebral glucose utilization was moderately and significantly reduced and by approximately the same degree in both groups of elderly subjects.

In table XVI.4, the originally heterogeneous asymptomatic disease group has been broken down into its major component subgroups. Of the total of 17 subjects in the group, 15 had been so classified because of evidence of vascular disease, namely hypertension or arteriosclerosis, or both. Of these, 5 had hypertension without any other evidence of disease. This meant that they fulfilled all the criteria of the normal elderly group except that their mean arterial blood pressure at the time of the cerebral blood flow determination was at least 3 standard deviations above the mean value observed in the normal young subjects. Ten subjects had

evidence of arteriosclerosis, about evenly divided between those with and those without hypertension, but, since there were no differences in cerebral circulatory and metabolic functions between normotensive and hypertensive arteriosclerotic subjects, all were grouped together in a single arteriosclerotic subgroup. The data obtained in the normal young subjects and the patients with chronic brain syndrome and psychosis are included in table XVI.4 for comparison.

It can be seen from the data in table XVI.4 that all the changes found in the asymptomatic disease group as a whole could be entirely accounted for by the findings in the arteriosclerotic subjects within that group. The nonarteriosclerotic hypertensives resembled the normal elderly subjects in all respects, except, of course, for their higher values of mean arterial blood pressure and cerebral vascular resistance. The arteriosclerotic subjects, however, had significant reductions in cerebral blood flow and cerebral venous pO_2; they were, in fact, almost exactly like the patients with chronic brain syndrome in all regards except for the absence of a significant decline in cerebral oxygen consumption. The changes in cerebral circulation and metabolism observed in the chronic brain syndrome patients were similar to those previously reported by Freyhan, Woodford and Kety (22).

The decreases in both cerebral blood flow and cerebral venous pO_2 point to cerebral circulatory insufficiency as the primary change in the circulatory and metabolic functions of the brain in arteriosclerotic subjects. The fact that cerebral oxygen consumption was not also reduced indicates that the degree of circulatory insufficiency, even though of the same degree as in the chronic brain syndrome patients, was itself not

TABLE XVI.3

Cerebral metabolism in normal young, normal elderly and elderly subjects with asymptomatic disease

Group	Number of Subjects	Oxygen Metabolism		Glucose Metabolism		Ratio of Oxygen to Glucose	Cerebral Respiratory Quotient
		$(A-V)_{O_2}$[1]	CMR_{O_2}[1]	$(A-V)_G$[1]	CMR_G[1]		
		volume %	*ml/100 gm./minute*	*mg. %*	*mg/100 gm./minute*	*moles/mole*	
Normal young	15	5.70 ± 0.30	3.5 ± 0.2	9.3 ± 0.8	6.0 ± 0.7	5.5 ± 0.5	0.92 ± 0.02
Normal elderly	26	5.88 ± 0.17	3.3 ± 0.1	8.2 ± 0.5	4.6 ± 0.2[2]	6.0 ± 0.2	0.91 ± 0.02
Elderly with miscellaneous asymptomatic disease	17	6.35 ± 0.37	3.2 ± 0.1	9.5 ± 0.9	4.8 ± 0.4[2]	5.7 ± 0.4	0.94 ± 0.02

[1] $(A-V)_{O_2}$, cerebral arteriovenous oxygen difference; CMR_{O_2}, cerebral oxygen consumption; $(A-V)_G$, cerebral arteriovenous glucose difference; CMR_G, cerebral glucose utilization

[2] Statistically significantly different from normal young subjects ($p < 0.05$).

TABLE XVI.4

Cerebral circulation and metabolism in normal young and elderly subjects, elderly subjects with asymptomatic vascular disease and patients with chronic brain syndrome and psychosis

Group	Number of Subjects	Age	Mean Arterial Blood Pressure	Cerebral Blood Flow	Cerebral Vascular Resistance	Cerebral Oxygen Consumption	Cerebral Venous Oxygen Tension
		years	*mm. Hg*	*ml./100 gm./minute*	*mm.Hg/(ml./100 gm./minute)*	*ml./100 gm./minute*	*mm. Hg*
Normal young	15	20.8 ± 0.4	84 ± 2	62 ± 3	1.3 ± 0.1	3.5 ± 0.2	38 ± 1
Normal elderly	26	71.0 ± 0.8[1]	93 ± 1[1]	58 ± 2	1.6 ± 0.1[1]	3.3 ± 0.1	36 ± 1
Elderly hypertensives without obvious arteriosclerosis	5	71.2 ± 1.4[1]	128 ± 11[1, 2]	55 ± 6	2.3 ± 0.1[1, 2]	3.6 ± 0.1	34 ± 3
Elderly with asymptomatic arteriosclerosis with or without hypertension	10	73.2 ± 0.8[1]	104 ± 2[1, 2]	48 ± 3[1, 2]	2.0 ± 0.2[1, 2]	3.2 ± 0.2	33 ± 2[1, 2]
Patients with chronic brain syndrome and psychosis	10	71.8 ± 1.8[1]	102 ± 6[1, 2]	48 ± 4[1, 2]	2.1 ± 0.3[1, 2]	2.7 ± 0.2[1, 2]	33 ± 1[1, 2]

[1] Statistically significantly different from normal young subjects ($p < 0.05$).

[2] Statistically significantly different from normal elderly men ($p < 0.05$).

TABLE XVI.5

Correlations between cerebral blood flow and metabolic rate and chronological age

Group	Number of Patients	Cerebral Blood Flow[1]	Cerebral Oxygen Consumption[1]
Normal elderly	26	−0.20	−0.10
Elderly with asymptomatic disease	17	−0.14	−0.44
Arteriosclerotic subgroup	9	−0.10	−0.68[2]
Nonarteriosclerotic subgroup	8	−0.18	−0.46

[1] Values are product moment correlation coefficients.

[2] Statistically significant ($p < 0.05$).

sufficient to limit the metabolism of the brain. It is interesting to speculate whether a prolonged period of moderately low cerebral blood flow caused by arteriosclerosis might not ultimately lead to tissue damage and the low cerebral oxygen consumption observed in the patients with chronic brain syndrome. The statistical data in table XVI.5 may have some bearing on this point. No statistically significant product-moment correlation coefficients between CBF or CMR_{O_2} and chronological age were observed in either the normal elderly or the total asymptomatic disease groups. When the asymptomatic disease group was divided into arteriosclerotic and nonarteriosclerotic subgroups, a relatively high and significant correlation between decline in CMR_{O_2} and chronological age was found in the arteriosclerotic subgroup. Since the subjects in this subgroup were already selected for the presence of arteriosclerosis, increased incidence of arteriosclerosis with advancing age cannot be a factor in the correlation. It would appear then that the correlation between decline in CMR_{O_2} and chronological age only in the presence of arteriosclerosis reflects either a greater severity or, more likely, a longer duration of the disease with increasing age.

DISCUSSION

The results of the present studies are consistent with the following conclusions about the normal process of aging in the human brain. Declines in cerebral blood flow and oxygen consumption are not the inevitable consequences of chronological aging or duration of life *per se*. When these changes occur in otherwise apparently healthy, or at least asymptomatic, elderly individuals, they are probably the result of vascular disease, arteriosclerosis in particular. Surprisingly minimal degrees of arteriosclerosis are sufficient to produce these changes; hypertension without arteriosclerosis has no such effects. The present findings clearly indicate that it is circulatory insufficiency which is the primary change. Indeed, in the asymptomatic arteriosclerotic subjects used in these studies no signifi-

cant reductions in cerebral oxygen consumption were observed, even though their cerebral blood flow, cerebral venous pO_2, and probably also tissue oxygen tension were reduced to the same low levels as existed in the patients with chronic brain syndrome and psychosis. It is a reasonable possibility that these arteriosclerotic subjects were still in a transition state before the chronic effects of the cerebral circulatory insufficiency and cerebral hypoxia resulted in sufficient tissue damage to be manifested by a reduction in cerebral oxygen consumption like that seen in the chronic brain syndrome patients. The significant negative correlation between cerebral oxygen consumption and chronological age only in the arteriosclerotic subjects (table XVI.5) suggests that it is not simply the presence of arteriosclerosis but its duration which is related to the decline in cerebral oxygen consumption. We are, therefore, essentially in agreement with Shenkin and his associates (7) and Bernsmeier (23), whose studies also indicated that the usually observed reductions in cerebral blood flow and oxygen consumption in later life (11) are not the consequences of the normal aging process but rather of arteriosclerosis.

The significance of the changes in cerebral glucose utilization observed in both the normal elderly group and the elderly subjects with asymptomatic disease is at present difficult to evaluate. Although CMR_{O_2} was essentially unchanged in either group, CMR_G was statistically significantly reduced in both and approximately to the same degree. This was an unexpected finding. Normally oxygen and glucose are consumed by the brain in almost stoichiometric amounts (24, 25), and, except in rare instances such as insulin hypoglycemia (26), CMR_{O_2} and CMR_G vary together, and both are measures of the cerebral metabolic rate. In our laboratory, and probably in most laboratories, CMR_{O_2} can be determined with far greater accuracy and precision than CMR_G, and it would, therefore, be surprising if the CMR_G turned out to be the more sensitive indicator of a change in cerebral metabolic rate. It is possible that there is in the aged a subtle metabolic change in the brain resulting in an impairment of cerebral glucose utilization which is not reflected in the oxygen consumption. There were no significant changes in CRQ (table XVI.3) to indicate any change in the nature of the substrate oxidized, but normally there is more glucose consumed by the brain than can be accounted for by its oxygen consumption (25). Assuming complete oxidation of the glucose to carbon dioxide and water, the theoretical molar ratio of oxygen consumption to glucose utilization would be 6.0. Normally this ratio is lower because of the excess glucose consumed, but there appears to be a tendency, though not statistically significant, for this ratio to rise in the aged (table XVI.3). It is, therefore, possible that the impairment is in the pathways of utilization of the extra glucose

which would then not be reflected in either the CRQ or the oxygen consumption. Unfortunately, previous studies of cerebral circulation and metabolism in the aged did not include measurements of CMR_G, and further speculation about this possibility is probably premature until the experimental finding is confirmed by additional experiments.

The validity of the conclusions drawn from these studies is to a great extent dependent on the effectiveness of the medical selection procedures in controlling the influences of age-associated disease. The recognition of arteriosclerosis and its distinction from normal aging processes is at best an extremely difficult undertaking, and we have no assurances that we were completely successful in accomplishing it. Undoubtedly there were individuals in the normal elderly group with unrecognized arteriosclerosis of a more significant degree than some of the individuals classified as arteriosclerotic in the asymptomatic disease group. Nevertheless, the methods of medical evaluation, as imprecise as they may be, if they have any virtues at all, must have at least some usefulness in distinguishing on the average between relative levels of health, even as regards arteriosclerosis. It may be argued that it is impossible to obtain elderly subjects with no arteriosclerosis. Our experience indicates that it is indeed a rare situation, and we were able to obtain the relatively few subjects for these studies only by a painstaking search among many volunteers over a period of 2 years. Even then we doubt that we were able to control completely the presence of arteriosclerosis, but we feel reasonably assured that all of our subjects were healthier than average individuals of the same age and that our normal elderly group as a whole was healthier than the subjects in the asymptomatic disease group. It was chiefly in regard to the rigorousness of the selection process that these studies differed from previous studies of this problem. The results tend to confirm the validity of the medical evaluation procedures. Although the research data were not used in the classification of the subjects, the results of the investigations in the various areas—cerebral circulation and metabolism, electroencephalography, cognitive and perceptual psychology, social psychology and psychiatry—tended to confirm the superior status of the normal elderly group and the lesser performance of the asymptomatic disease group (12).

It must be pointed out that the methods employed in these studies describe only the blood flow and metabolism of a representative fraction of the brain taken as a whole. They give no information concerning these functions in the total brain, and, if there were changes in brain weight with age, there might be changes in total cerebral blood flow and metabolism not detected by our studies. Furthermore, there may be age changes within the brain which are not reflected in the cerebral blood

flow and metabolic rate. Therefore, despite our findings that these functions change only when arteriosclerosis is present, it would be an unjustifiable extrapolation to conclude that it is this condition which is responsible for aging of the brain. Indeed, even in our normal elderly subjects, in whom we found no significant changes in cerebral blood flow and oxygen consumption, evidence of impairment of cognitive and perceptual functions (27–29) and a decrease in the peak frequency of the EEG (30) were observed, although not nearly so clearly as in the arteriosclerotic subjects. These changes may have been the result of unrecognized disease, or they may indicate degradative changes not related to the cerebral circulation and metabolism. The results of the present studies do suggest, however, that even if the brain ages independently of the circulation, when vascular disease develops, it becomes the pacemaker of the aging process within the brain.

SUMMARY

1. Studies of the cerebral circulation and metabolism revealed no significant differences in cerebral blood flow and oxygen consumption between a group of normal young subjects (mean age = 20.8 years) and a group of highly selected normal elderly men (mean age = 71.0 years) who were functioning effectively in their communities and were as free of evidence of disease, including vascular disease, as was possible to obtain in their age group.

2. In a similar group of elderly men differing from the previous one only in that they exhibited clear evidence of minimal asymptomatic disease, chiefly vascular, there was a statistically significant decline in cerebral blood flow of approximately 15 per cent. Cerebral oxygen consumption and cerebral venous pO_2 also tended to be lower but not statistically significantly.

3. All of the changes in cerebral blood flow, oxygen consumption and cerebral venous pO_2 in the elderly asymptomatic disease group could be accounted for by the results obtained in the arteriosclerotic subjects within that group. In fact, cerebral blood flow and cerebral venous pO_2 in the arteriosclerotic subjects were significantly reduced to the same levels observed in patients with chronic brain syndrome and psychosis. Cerebral oxygen consumption also tended to be lower in the arteriosclerotic subjects although not statistically significantly and not nearly to the same degree as in the chronic brain syndrome patients. Hypertensives without arteriosclerosis were normal with regard to all these functions.

4. The reductions in cerebral blood flow and cerebral venous pO_2 without a proportionate decrease in cerebral oxygen consumption indi-

cated a primary circulatory insufficiency and cerebral hypoxia in the arteriosclerotic subjects. A statistically significant correlation between decline in cerebral oxygen consumption and chronological age only in the arteriosclerotic subjects suggested an increasing tendency toward impairment of cerebral metabolism with increasing duration of the disease.

5. Although cerebral oxygen consumption was not statistically significantly decreased in either the normal elderly or the elderly asymptomatic disease group, cerebral glucose utilization was markedly reduced in both. The possible implications of this discrepancy between the two cerebral metabolic rates have been discussed.

6. It was suggested that decreases in cerebral blood flow and oxygen consumption are not the consequences of chronological aging *per se* but rather of arteriosclerosis, which causes first a relative cerebral circulatory insufficiency and hypoxia and then ultimately, after a protracted period of the latter, cerebral tissue damage and a reduction in cerebral metabolic rate.

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DISCUSSION

DR. IRVING WRIGHT: It is of interest that I had an occasion to visit Dr. Nylin's laboratory shortly before his unfortunate death, and he had very interesting evidence that what Dr. Sokoloff said was true in relation to the cerebral circulation: namely, in patients who are otherwise normal—I believe the oldest one whose chart he showed me was 83—there was no measured difference in the circulation, that is, by his technique as compared with the circulation of young individuals.

The question I would like to ask Dr. Sokoloff, however, is a little bit different. Maybe I didn't understand his classification, but I am interested to know how he decided that these patients with no symptoms had cerebral atherosclerosis, whether this classification was made before or after the test and what the criteria were.

DR. LOUIS SOKOLOFF: These particular studies were part of a very large multidisciplinary study that was going on at the National Institute of Mental Health involving many investigators from many disciplines. There was a separate medical staff that handled the patients and did the clinical work on them. All the data was turned over to the statistical branch without communications among the various investigators, so that we had no idea what the classifications of the patients were until some time after the studies were done.

The clinicians and all the physicians involved ultimately decided the classification on the basis of the findings. We did not exclude only patients with cerebral arteriosclerosis. We assumed that arteriosclerosis is a generalized vascular disease, and if we found good evidence of it in any area, we excluded the patient, regardless of whether we thought it was in the brain.

The only finding about which we compromised was the finding of evidence of retinal arteriosclerosis on the basis of ophthalmoscopic examination. All but five of the subjects that we saw showed this.

DR. IRVING WRIGHT: Did you find as Professor Nylin did, that patients with Alzheimer's syndrome showed a marked decrease in their cerebral blood flow?

DR. LOUIS SOKOLOFF: Anyone with Alzheimer's syndrome would have been excluded from this study. I have done one study on an Alzheimer's patient, confirmed by several biopsies, and in that case, there was a reduction in both cerebral blood flow and cerebral oxygen consumption; the cerebral oxygen tension was inde-

cisive. I don't know what the primary defect was. The patient was almost like our chronic brain syndrome patients, except that the cerebral venous oxygen tension wasn't quite as low.

To continue the description of the diagnostic criteria, hypertension was determined by ascultatory blood pressure or by means of a femoral arterial needle and a mercury manometer at the time of the study. Our diagnosis of hypertension was based on a mean blood pressure 3 standard deviations above the mean for normal young subjects with an average age of 21. It was decided on this definition to avoid the problem of how one defines clinical hypertension.

The diagnosis of arteriosclerosis was made on the basis of electrocardiogram abnormalities, conductive defects or evidence of an old myocardial infarction, absent peripheral pulses, x-ray evidence of vascular calcification in the aorta or the carotid siphon, or aortic dilatation. Retinal arteriosclerosis, as I said, appeared in all but, I think, five subjects. There were one or two subjects with minimal Parkinsonism which was attributed to cerebral arteriosclerosis—very minimal. There were patients with duodenitis, questionable peptic ulcer and so on.

No single finding was considered essential for the diagnosis of arteriosclerosis. Each finding was weighted differently by the physicians in the project. I do not think at all that our normal elderly group was completely arteriosclerosis-free; in fact, I would believe that each elderly subject had a little. But I think by rigorously applying a set of criteria with only some slight moderation, we did obtain a group of elderly people who were normal enough to have normal cerebral blood flow and oxygen consumption, in spite of the probable presence of a small amount of arteriosclerosis.

DR. CLARK MILLIKAN: Are there any further questions? Dr. Scheinberg.

DR. PERITZ SCHEINBERG: Dr. Millikan, I would like to make just one or two comments. I can appreciate Dr. Sokoloff's difficulty in attempting to assess this problem. A number of years ago, we published a study, and after thinking about it for a number of years thereafter, I have had some diffculty in evaluating what we originally did. Our findings suggested when we originally studied cerebral blood flow in the aged as compared with those with known cerebrovascular disease that in a given age group there was really very little difference between the measured cerebral blood flow and metabolic blood values in individuals with proven cerebrovascular disease unless there was a significant alteration in mental status, which is another way of saying that in those individuals who had alterations in mental status there was probably more advanced or progressive disease.

We used as a criteria for atherosclerosis the existence of a previous stroke and the existence of diabetes and frequently hypertension.

I would like to emphasize the difficulty of this problem by mentioning a recent experience. Dr. Reinmuth and I studied a patient who had recurrent ischemic attacks which were about as classical as any we had ever seen and which occurred on standing upright. This man had, at the bifurcation of his common carotid artery, a large atherosclerotic plaque which almost completely occluded the internal carotid artery—only a trickle of blood passed through that area, at least a trickle of dye.

During the study of blood flow, the opposite common carotid and internal carotid arteries were compressed. This was done to see what reduction in cerebral blood flow would occur under these circumstances.

To our great surprise, there was no change at all, suggesting that there are undoubtedly many, many ways in which blood gets into the brain. I would like to point out again the usefulness and value in a technique which permits rapid measurement of cerebral blood flow in this particular kind of observation. I am convinced that there is much to be learned about the dynamics of cerebrovascular disease by this kind of study.

DR. LOUIS SOKOLOFF: About the question of the relationship of the reduction of cerebral blood flow and oxygen consumption with change in mental status, I don't think that there was very much difference in mental status between the two groups of elderly here; but then there was no significant difference in oxygen consumption.

I agree that when there is a change in cerebral oxygen consumption, there is likely to be also an associated change in mental status.

This asymptomatic disease group here represents a transition group where they have a little bit more arteriosclerosis than the normal elderly group, but they have not yet had the consequences of it. One could expect that these subjects would show a change in mental status sooner than the normal elderly group.

DR. RAYMOND D. ADAMS: Dr. Sokoloff has undertaken an extraordinarily difficult problem. The validity of his interpretations really stands or falls according to the formation of his groups. The collateral evidence that this group is arteriosclerotic merely because there is some evidence of peripheral vascular disease outside the cerebral circulation will inevitably be open to question. Just from the strictly neuropathological side the accuracy of all of the finest clinical assessments of the existence of cerebrovascular disease is notoriously unreliable. Again and again we have seen this diagnosis made by expert clinicians only to discover that there is not a speck of atherosclerosis to be found at autopsy.

The question really comes as to whether or not this group that is called chronic arteriosclerotic is any different, except quantitatively, than the one that shows this chronic mental syndrome.

What were the criteria for differentiating those two groups? Also, there is a technique problem here. There is a pretty definite fall-off in brain weight that goes on with age, as everyone knows. Are the figures for cerebral metabolism really corrected for some kind of predicted fall-off. Could this failure to allow for this account for any of the difference that is going on even in those that seem to be relatively asymptomatic at 65 or 70?

DR. CLARK MILLIKAN: Would you respond to these last two particular questions?

DR. LOUIS SOKOLOFF: I am not sure I understand the question about how we distinguished the last two groups. Which groups are you referring to?

DR. RAYMOND D. ADAMS: The group with the chronic brain syndrome from those with arteriosclerotic, asymptomatic arteriosclerotic disease. Is there really a difference between these two groups and between normals?

DR. LOUIS SOKOLOFF: There is a difference in their mental status. The chronic

brain syndrome patients were hospitalized for chronic brain syndrome with psychosis while the arteriosclerotic subgroups and all the other subjects were drawn from the community, were functioning normally, and were not psychotic.

Also, the latter did not have as severe a degree of arteriosclerosis as the chronic brain syndrome cases because severe arteriosclerosis with symptoms were excluded from the study. We tried originally to have the same kind of standards for the chronic brain syndrome patients, but we would hardly have been able to get any group at all if we had excluded severe arteriosclerosis in the patient group.

As for the question of brain weight, this was the nitrous oxide technique which was used, and that measures the blood flow in an average fraction of the brain taken as a whole. It has no bearing at all on the total blood flow or total oxygen consumption of the brain as a whole, and it would not give any information at all on what happens with the change in brain weight.

The data obtained with the nitrous oxide method have relevance to the circulatory and metabolic functions at the tissue level. The change in brain weight might have more to do with psychiatric aspects, mental status, and so on. A change in total blood flow might not mean a thing as far as what is happening at the local level; each gram of tissue might still be getting the same blood flow and having the same oxygen consumption, but there might be just less tissue.

DR. RAYMOND D. ADAMS: But part of the brain weight of your arteriosclerotic group was about 1300 and that of your other group was 1225. How would that affect your figures?

DR. LOUIS SOKOLOFF: It would not affect our figures at all because we measured blood flow or O_2 consumption per 100 grams of existing brain tissue.

DR. RAYMOND A. ADAMS: But how do you know what the existing brain tissue is in this case?

DR. LOUIS SOKOLOFF: We don't have to. The method gives you that answer directly in milliliters per 100 grams of brain tissue. We don't divide by brain weight to get that value.